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Thomas Jovin

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EXAMINER

STRZELECKA, TERESA E

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/568,038	Applicant(s) JOVIN ET AL.	
	Examiner TERESA E. STRZELECKA	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 June 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 17 and 18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 17 and 18 is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to an amendment filed June 16, 2010. Claims 1-13 were previously pending. Applicants added new claims 17 and 18. Claims 1-13, 17 and 18 are pending and will be examined.
2. All of the previously presented rejections with respect to claims 1-13 are maintained, since Applicants did not amend any of these claims. Applicants' arguments regarding the rejection of claims 1-13 under 35 U.S.C. 112, first paragraph, scope of enablement, were addressed previously. Regarding the rejections of claims 1-3 and 7-13 under 35 U.S.C. 103(a) over Gadella et al., Song et al., and the rejection of claims 4-6 under 35 U.S.C. 103(a) over Gadella et al., Song et al. and Watrob et al., Applicants traverse the rejections in view of claims 17 and 18. However, claims 17 and 18 are new and were not rejected over the above references. Since claim 1 was not amended, the rejections are maintained.
3. The newly added claims 17 and 18 are allowed since no references were found teaching or suggesting the claims.

Claim Interpretation

4. The term "characteristic kinetic quantity of a chemical reaction" has not been defined by Applicants, therefore it is interpreted as any measurable variable.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monitoring chemical reactions in which the chemical species are fluorophores themselves and in which the physical or chemical properties of the fluorophores are

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changed upon irradiation with light in such a way as to create populations of molecules in two different states where the populations of molecules are different from the populations before the irradiation, does not reasonably provide enablement for monitoring chemical reactions with any molecule having a fluorophore attached to it in any other chemical reaction. In addition, there is no enablement for determining any kinetic quantity of any chemical reaction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

Claims 1-13 are broadly drawn to a method for determining a characteristic kinetic quantity of a chemical reaction in a sample

wherein said chemical reaction involves a plurality of chemical species, at least a first one of said species including one a fluorophore being a FRET acceptor of a FRET pair consisting of a FRET donor and a FRET acceptor and a at least a second one of said species including a fluorophore being a FRET donor of said FRET pair,

said acceptor being a photochrome, the absorption spectrum of which being changeable by irradiation with light of a suitable wavelength, and

said donor being a fluorophore, the emission spectrum of which having an overlap region with said FRET acceptor's absorption spectrum, the size of said overlap region being dependent on the photochromic state of said FRET acceptor,

wherein said chemical reaction reversibly converts said first and second species as free ligands into at least one product comprising a combination of said first and second species, the method comprising the steps of:

having light of a wavelength capable of switching said photochromic state of said FRET acceptor impinge on said sample with the chemical reaction being in its equilibrium state, thereby switching said photochromic state of said acceptor in said product of said chemical reaction less efficiently than in said free ligand, thus a non-equilibrium state of said chemical reaction, and

observing, by means of a FRET dependent fluorescence signal of at least one of said fluorophore and said acceptor at least one temporal portion of a relaxation of concentrations of said species involved.

However, as will be further discussed, there is no support in the specification and prior art for the full scope of the claimed method. The invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of how to determine any kinetic parameters of any chemical reaction, even one involving just fluorophores themselves. There are no examples of

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how to determine kinetic parameters of any other reaction in which molecules are labeled with fluorophores.

Guidance in the Specification.

The specification provides no evidence that the disclosed use of photochromic FRET acceptor molecules provides means for detecting any kinetic quantity of a chemical reaction, for example, a rate constant. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. Applicants did not show that light can cause deviation from equilibrium concentrations of any chemical species in any chemical reaction in which the products are labeled with photochromic acceptors, except the photochromic acceptors themselves.

The unpredictability of the art and the state of the prior art

The only example found in literature for use in determining reaction rates is Giordano et al. (J. Am. Chem. Soc., vol. 124, pp. 7481-7489, 2002; cited in the IDS), in which the photoconversion rates of diheteroarylethene compounds bound to Lucifer Yellow cadaverine were determined using light-induced conversion of diheteroarylethene between two different states, open and closed.

There are no examples in literature how light irradiation could cause a change in concentration of chemical reaction participants in any reaction which does not involve the photochromic acceptors themselves, since even in the case of the acceptors attached to a DNA, for example, irradiating the reaction with light would cause a change in the state of the acceptors, but not in the state of the DNA molecules to which they were attached, i.e., in the case of hybridization reaction between a population of DNA molecules labeled with an acceptor and a second population labeled with a donor, irradiating the reaction with light would not change the concentrations of

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these two types of DNA populations. Therefore, the rate constants for hybridization could not be determined from such measurement. Further examples of macromolecular systems in which such process would not work are protein-DNA binding, for example, as presented by Kozlov et al. (Biochemistry, vol. 41, pp. 6032-6044, 2002; cited in the previous office action), protein-substrate interactions, as detailed by Takakusa et al. (J. Am. Chem. Soc., vol. 124, pp. 1653-1657, 2002; cited in the previous office action) or protein-membranes interactions, as referenced by Hamman et al. (J. Biomol. Screening, vol. 7, pp. 45-55, 2002; cited in the previous office action). Since there are literally billions of potential chemical reactions using molecules labeled with fluorescent donors and acceptors, the above examples are only a minute fraction.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to detection of kinetic parameters of any chemical reaction in which participating molecules are labeled with fluorescent acceptor and donor molecules, including determining which molecules aside from the photochromes themselves undergo physical or chemical changes in the presence of light of any wavelength, and how such kinetic constants can be determined. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the kinetic parameters of a large percentage of chemical reactions cannot be measured by perturbing the equilibrium state of the reaction with light, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3 and 7-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gadella et al. (J. Cell Biol., vol. 129, pp. 1543-1558, 1995; cited in the previous office action) and Song et

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al. (J. Photochem. Photobiol., vol. 150, pp. 177-185, July 26, 2002; cited in the previous office action).

A) Regarding claim 1, Gadella et al. teach detection of oligomerization of the epidermal growth factor (EGF) molecules in a reaction involving free EGF molecules labeled with fluorophores (Abstract):

wherein said chemical reaction involves a plurality of chemical species, at least a first one of said species including one a fluorophore being a FRET acceptor of a FRET pair consisting of a FRET donor and a FRET acceptor and a at least a second one of said species including a fluorophore being a FRET donor of said FRET pair (page 1545, second paragraph, where the first species is EGF labeled with fluorescein (donor) and the second species is EGF labeled with tetramethyl-rhodamine (acceptor),)

said donor being a fluorophore, the emission spectrum of which having an overlap region with said FRET acceptor's absorption spectrum (page 1544, last paragraph),

wherein said chemical reaction reversibly converts said first and second species as free ligands into at least one product comprising a combination of said first and second species (page 1545, fourth paragraph; page 1548, fourth and fifth paragraph; page 1549, first and second paragraph; page 1554, third paragraph; where the free EGF molecules are converted into a dimer), the method comprising the steps of:

having light of a wavelength capable of switching said photochromic state of said FRET acceptor impinge on said sample with the chemical reaction being in its equilibrium state (page 1545, fifth and sixth paragraph; page 1548, paragraphs 3-5; Fig. 3-5), and

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observing, by means of a FRET dependent fluorescence signal of at least one of said fluorophore and said acceptor at least one temporal portion of a relaxation of concentrations of said species involved (page 1545, fifth and sixth paragraph; page 1548, paragraphs 3-5; Fig. 3-5).

Regarding claim 2, Gadella et al. teach detecting fluorescence of the donor (page 1545, sixth paragraph; page 1548, third paragraph).

Regarding claim 10, Gadella et al. teach excitation of FRET acceptor with visible light (page 1545, fifth paragraph).

B) Gadella et al. do not teach the acceptor being a photochromic molecule or observing FRET effect between switched states of the photochromic acceptor and a fluorescent donor.

C) Regarding claim 1, Song et al. teach a photochromic acceptor molecule which can act as a light-induced switch in FRET (Abstract; page 178, third and last paragraph; page 179-181; page 182, paragraphs 1-3).

Regarding claim 3, Song et al. teach measuring fluorescence of the photochromic acceptor (page 179, third paragraph; page 180, fourth paragraph; Fig. 2).

Regarding claims 7-10, Song et al. teach switching the photochromic acceptor between the ON and OFF states using two different wavelengths, one of them being in the UV region and the other in the visible region (page 178, third paragraph; page 179, third paragraph; Fig. 2).

Regarding claim 11, Song et al. teach the intensity of irradiation for the photochromic effect being higher than the intensity of irradiation to observe the fluorescence (page 179, third and fourth paragraphs).

Regarding claims 12 and 13, Song et al. teach irradiating the sample in an alternating (= temporarily modulated) fashion to change the photochromic effect of the acceptor (page 182, last two paragraphs; Fig. 5; page 183, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the photochromic acceptor of Song et al. in the method of FRET microscopy of Gadella et al. The motivation to do so is expressly provided by Song et al., who state (page 178, second and third paragraphs; page 184, last paragraph):

"For static systems under cellular fixation, the pbFRET techniques are simple and useful [28–31]. However, photobleaching rates are linear or more complex [21] functions of irradiance and dependent on environmental parameters such as the local redox state [32,33]. In addition the photodestruction of donor or acceptor precludes the possibility of multiple FRET measurements at a given spatial location.

Our aim was to design a method that offers an intrinsic internal reference and the possibility for continued and repeated determinations of the FRET process. Photochromic compounds can be exploited to achieve this goal. Photochromism is the light-induced transformation of a single chemical species between two isomeric structures with distinct absorption spectra [34–37]. Near-ultraviolet irradiation induces reversible changes in the structure and absorption properties of a photochromic molecule from an initial colorless to a colored form. Only the latter has an absorption band overlapping the emission band of a selected donor and is thereby able to potentiate energy transfer. Subsequent irradiation in the visible absorption band of the colored form reverts it to the initial colorless form and disables the FRET process, thus supplying the required internal reference state. The FRET efficiency can be derived simply from the fractional change in donor fluorescence or donor lifetime for each pixel position."

"The photoreversibility of the photochromic acceptor offers a unique opportunity for performing repeated quantitative FRET observations under the unknown stoichiometry of the donor–acceptor relationships prevailing in microscopy experiments. A photochromic acceptor

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offers the critical internal control (acceptor-free donor) within the same sample preparation and at every spatial location and chemical environment."

10. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gadella et al. (J. Cell Biol., vol. 129, pp. 1543-1558, 1995; cited in the previous office action) and Song et al. (J. Photochem. Photobiol., vol. 150, pp. 177-185, July 26, 2002; cited in the previous office action), as applied to claim 1 above, and further in view of Watrob et al. (J. Am. Chem. Soc., vol. 125, pp. 7336-7343, May 2003; cited in the previous office action).

A) Regarding claims 4-6, Giordano et al. teach a system with one acceptor and one donor, but do not teach a system with an additional acceptor.

B) Regarding claims 4-6, Watrob et al. teach using a system with one donor and two acceptors (Scheme 1; page 7337, 7338).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used additional acceptor of Watrob et al. in the method of Gadella et al. and Song et al. The motivation to do so is provided by Watrob et al., who state (page 7342, last paragraph):

"Three-chromophore FRET systems offer several advantages. First, three-chromophore systems report the simultaneous proximity of three species and provide the ability to measure two or three distances in a complex. Structural information about the assembly can then be inferred from the relative positions of individual components of the complex. For example, in Case I where no FRET1 \rightarrow 3 occurs, r_{13} must be $>1.5 R_{013}$. This restricts the position of **3** relative to **1** to a minimal distance of $r_{13} \sim 1.75 R_{013}$ and a maximal distance of $r_{13} = r_{12} + r_{23}$ for a linear arrangement of **1**, **2**, and **3**. Second, in the case of linear or near linear arrangement of the three chromophores, two-step FRET extends the distance range for detection of simultaneous proximity. For example, assuming $R_0 = 55 \text{ \AA}$ for the two FRET pairs and a detection limit of $1.5 R_0$, one-step FRET at a distance $r = 83 \text{ \AA}$ has an efficiency $E_{ij} = 0.08$. A two-step FRET relay with $E_{\text{relay}} = 0.08$ corresponds to a total

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distance $r = 127 \text{ \AA}$. Thus, the detectable distance range increases by as much as 50%. Third, three-chromophore systems require fewer labeled samples to measure two or three distances than conventional one-step FRET.”

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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